

AMENDMENTS TO THE CLAIMS:

Please amend the claims as follows:

1. (Currently Amended) An isolated HBV polynucleic acid ~~or a fragment thereof~~, said polynucleic acid ~~or said fragment~~ characterized in that it comprises codon 204 of the HBV reverse transcriptase domain wherein said codon 204 is encoding a serine.

2. (Currently Amended) The HBV polynucleic acid ~~or fragment thereof~~ according to claim 1, said polynucleic acid ~~or fragment~~ further characterized in that it comprises codon 180 of the HBV reverse transcriptase domain wherein said codon 180 is encoding a methionine.

3. (Currently Amended) The HBV polynucleic acid ~~or fragment thereof~~ according to claim 1 which is defined by SEQ ID NO:6 or the complement thereof.

4. (Currently Amended) An isolated HBV DNA polymerase/reverse transcriptase protein ~~or a fragment thereof~~, said protein ~~or fragment~~ characterized in that it comprises amino acid 204 of the HBV reverse transcriptase domain and wherein said amino acid 204 is a serine.

5. (Currently Amended) The HBV DNA polymerase/reverse transcriptase protein ~~or fragment thereof~~ according to claim 4 characterized further in that it comprises amino acid 180 of the HBV reverse transcriptase domain and wherein said amino acid 180 is a methionine.

6. (Currently Amended) An isolated HBV DNA polymerase/reverse transcriptase protein ~~or a fragment thereof~~, said protein ~~or fragment~~ characterized in that it comprises amino acid 204 of the HBV reverse transcriptase domain and wherein said amino acid

204 is a serine, said protein ~~or fragment thereof~~ being encoded by the isolated HBV polynucleic acid ~~or fragment thereof~~ according to one of claims 1 to 3.

7. (Currently Amended) The HBV DNA polymerase/reverse transcriptase protein ~~or fragment thereof~~ according to claim 4 which is defined by SEQ ID NO:4, ~~or a fragment thereof.~~

8. (Currently Amended) An isolated HBV variant ~~Hepatitis B virus~~ comprising a polynucleic acid ~~or fragment thereof~~ according to claim 1.

9. (Currently Amended) An isolated HBV variant ~~Hepatitis B virus~~ comprising a protein ~~or fragment thereof~~ according to claim 4.

10. (Currently Amended) A vector comprising the HBV polynucleic acid ~~or fragment thereof~~ according to claim 1.

11. (Currently Amended) A host cell comprising the HBV polynucleic acid ~~or fragment thereof~~ according to claim 1, ~~[[an]]~~ a variant Hepatitis B virus containing said polynucleic acid ~~or fragment thereof~~ or a vector containing said polynucleic acid ~~or fragment thereof~~.

12. (Currently Amended) A host cell comprising the HBV DNA polymerase/reverse transcriptase protein ~~or fragment thereof~~ according to claim 4 or ~~[[an]]~~ a variant Hepatitis B virus containing said HBV DNA polymerase/reverse transcriptase protein ~~or fragment thereof~~.

13. (Currently Amended) A method for detecting the presence of an HBV in a biological sample, said method comprising the step of detecting the presence of an HBV polynucleic acid ~~or fragment thereof~~ according to claim 1.

14. (Original) The method according to claim 13 comprising:

(i) obtaining a target HBV polynucleic acid from said biological sample wherein said target HBV polynucleic acid is suspected to comprise a serine-encoding codon 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon 180 and a serine-encoding codon 204 of the HBV reverse transcriptase domain;

(ii) obtaining the nucleic acid sequence of the target HBV polynucleic acid of (i);

(iii) inferring, from the nucleic acid sequence obtained in (ii), the presence of said serine-encoding codon 204 of the HBV reverse transcriptase domain or of said methionine-encoding codon 180 and said serine-encoding codon 204 of the HBV reverse transcriptase domain and, therefrom, the presence of said HBV in said biological sample.

15. (Currently Amended) The method according to claim[[s]] 13 comprising:

(i) obtaining a target HBV polynucleic acid from said biological sample wherein said target HBV polynucleic acid is suspected to comprise a serine-encoding codon 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon 180 and a serine-encoding codon 204 of the HBV reverse transcriptase domain;

(ii) contacting the target HBV polynucleic acid of (i) with an oligonucleotide capable of discriminating a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine resulting in a discriminatory signal relating to codon 204, or with an oligonucleotide capable of discriminating a codon 180 encoding a methionine from a codon 180 encoding a leucine resulting in a discriminatory signal relating to codon 180 and an oligonucleotide capable of discriminating a codon 204

encoding a serine from a codon 204 encoding a methionine, valine or isoleucine
resulting in a discriminatory signal relating to codon 204;

(iii) inferring, from the discriminatory signal obtained in (ii), the presence of said serine-encoding codon 204 of the HBV reverse transcriptase or of said ~~discriminatory signals relating to codon 204 and to codon 180 obtained in (ii)~~ of said methionine-encoding codon 180 and said serine-encoding codon 204 of the HBV reverse transcriptase domain and, therefrom, the presence of said HBV in said biological sample.

16. (Original) The method according to claim 15 wherein said discriminating in (ii) is based on hybridization and wherein said discriminatory signal in (iii) is a hybridization signal.

17. (Currently Amended) A method for detecting resistance to lamivudine or a combination of antiviral drugs comprising lamivudine ~~an antiviral drug of an~~ HBV virus present in a biological sample, said method comprising the step of detecting the presence of an HBV polynucleic acid ~~or fragment thereof~~ according to claim 1.

18. (Currently Amended) The method according to claim 17 comprising:

(i) obtaining a target HBV polynucleic acid from said biological sample wherein said target HBV polynucleic acid is suspected to comprise a serine-encoding codon 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon 180 and a serine-encoding codon 204 of the HBV reverse transcriptase domain;

(ii) obtaining the nucleic acid sequence of the target HBV polynucleic acid of (i);

(iii) inferring, from the nucleic acid sequence obtained in (ii), the presence of said serine-encoding codon 204 in the HBV reverse transcriptase domain or of said methionine-encoding codon 180 and said serine-encoding codon 204 in the HBV reverse transcriptase domain and, therefrom, said resistance to lamivudine or a combination of antiviral drugs comprising lamivudine ~~an antiviral drug of an~~ HBV virus present in said biological sample.

19. (Currently Amended) The method according to claim 17 comprising:

(i) obtaining a target HBV polynucleic acid from said biological sample wherein said target HBV polynucleic acid is suspected to comprise a serine-encoding codon 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon 180 and a serine-encoding codon 204 of the HBV reverse transcriptase domain;

(ii) contacting the target HBV polynucleic acid of (i) with an oligonucleotide capable of discriminating a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine resulting in a discriminatory signal relating to codon 204,

or with an oligonucleotide capable of discriminating a codon 180 encoding a methionine from a codon 180 encoding a leucine resulting in a discriminatory signal relating to codon 180 and an oligonucleotide capable of discriminating a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine resulting in a discriminatory signal relating to codon 204;

(iii) inferring, from the discriminatory signal obtained in (ii), the presence of said serine-encoding codon 204 in the HBV reverse transcriptase domain or of said

~~discriminatory signals relating to codon 204 and to codon 180 obtained in (ii) of said~~
methionine-encoding codon 180 and said serine-encoding codon 204 in the HBV
reverse transcriptase domain and, therefrom, said resistance to lamivudine or a
combination of antiviral drugs comprising lamivudine ~~an antiviral drug of an~~ HBV virus
present in said biological sample.

20. (Original) The method according to claim 19 wherein said discriminating in (ii)
is based on hybridization and wherein said discriminatory signal in (iii) is a hybridization
signal.

21. (Currently Amended) A diagnostic kit for detecting the presence of an HBV in
a biological sample, said kit comprising a means for detecting the presence of an HBV
polynucleic acid ~~or fragment thereof~~ according to claim 1.

22. (Currently Amended) The diagnostic kit according to claim 21 comprising:

(i) optionally, a means for obtaining the nucleic acid sequence of a target HBV
polynucleic acid suspected to comprise a serine-encoding codon 204 of the HBV
reverse transcriptase domain or to comprise a methionine-encoding codon 180 and a
serine-encoding codon 204 of the HBV reverse transcriptase domain; and

(ii) a means for inferring, from the nucleic acid sequence obtained in (i), the
presence of said serine-encoding codon 204 of the HBV reverse transcriptase domain
or of said methionine-encoding codon 180 and said serine-encoding codon 204 of the
HBV reverse transcriptase domain and, therefrom, the presence in said biological
sample of said HBV.

23. (Original) The diagnostic kit according to claim 21 comprising an oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine.

24. (Original) The diagnostic kit according to claim 23 further comprising an oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 180 encoding a methionine from a codon 180 encoding a leucine.

25. (Currently Amended) A diagnostic kit for detecting resistance to lamivudine or a combination of antiviral drugs comprising lamivudine~~an antiviral drug~~ of an HBV virus present in a biological sample, said kit comprising a means for detecting the presence of an HBV polynucleic acid ~~or fragment thereof~~ according to claim 1.

26. (Currently Amended) The diagnostic kit according to claim 25 comprising:

(i) optionally, a means for obtaining the nucleic acid sequence of the target HBV polynucleic acid suspected to comprise a serine-encoding codon 204 of the HBV reverse transcriptase domain or to comprise a methionine-encoding codon 180 and a serine-encoding codon 204 of the HBV reverse transcriptase domain; and

(ii) a means for inferring, from the nucleic acid sequence obtained in (i), the presence of said serine-encoding codon 204 in the HBV reverse transcriptase domain or of said methionine-encoding codon 180 and said serine-encoding codon 204 in the HBV reverse transcriptase domain and, therefrom, resistance to lamivudine or a combination of antiviral drugs comprising lamivudine~~an antiviral drug~~ of an HBV virus present in said biological sample.

27. (Original) The diagnostic kit according to claim 25 comprising an oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine.

28. (Original) The diagnostic kit according to claim 27 further comprising an oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 180 encoding a methionine from a codon 180 encoding a leucine.

29. (Previously Presented) The diagnostic kit according to claim 27 further comprising a means for detecting a discriminatory signal obtained by contacting said HBV polynucleic acid and said oligonucleotide.

30. (Currently Amended) The diagnostic kit according to claim 27 wherein said oligonucleotide ~~[[are]]~~is attached or immobilized to a solid support.

31. (Withdrawn – Currently Amended) A method for detecting resistance to lamivudine or a combination of antiviral drugs comprising lamivudine ~~an antiviral drug of~~ an HBV virus present in a biological sample, said method comprising the step of detecting the presence of an HBV DNA polymerase/reverse transcript protein ~~or fragment thereof~~ according to claim 4.

32. (Withdrawn – Currently Amended) A method for screening for drugs active against an HBV virus comprising a polynucleic acid according to claim 1 or comprising a protein according to any of claims 4, 5 or 7 ~~encoded by said polynucleic acid~~, said method comprising:

- (i) measuring replication of said HBV virus in the absence of said drug;
- (ii) measuring replication of said HBV virus in the presence of said drug;

(iii) inferring from (i) and (ii) the inhibitory effect of said drug on replication of said HBV virus.

33. (Withdrawn) The method according to claim 32 further comprising performing steps (i), (ii) and (iii) with a wild-type HBV virus and comparing the inhibitory effect of said drug on replication of said wild-type HBV virus with the inhibitory effect of said drug on replication of the HBV virus comprising the polynucleic acid or comprising a DNA polymerase/reverse transcriptase protein encoded by said polynucleic acid.

34. (Withdrawn – Currently Amended) A method for screening for drugs active against an HBV virus comprising a polynucleic acid according to claim 1 or comprising a protein encoded by said poynucleic acid, said method comprising:

(i) measuring a DNA polymerase/reverse transcriptase activity of said HBV virus in the absence of said drug;

(ii) measuring the same DNA polymerase/reverse transcriptase activity as in (i) of said HBV virus in the presence of said drug;

(iii) inferring from (i) and (ii) the inhibitory effect of said drug on said DNA polymerase/reverse transcriptase activity of said HBV virus.

35. (Withdrawn) The method according to claim 34 further comprising performing steps (i), (ii) and (iii) with a wild-type HBV virus and comparing the inhibitory effect of said drug on said DNA polymerase/reverse transcriptase activity of said wild-type HBV virus with the inhibitory effect of said drug on said DNA polymerase/reverse transcriptase activity of the HBV virus comprising said polynucleic acid or comprising said DNA polymerase/reverse transcriptase protein.

Claim 36. (Canceled)

37. (Withdrawn - Currently Amended) An oligonucleotide capable of discriminating, in an HBV polynucleic acid or fragment thereof according to claim 1, a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine in the HBV reverse transcriptase domain.

38. (Previously Presented) The diagnostic kit according to claim 28 further comprising a means for detecting a discriminatory signal obtained by contacting said HBV polynucleic acid and said oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine and means for detecting a discriminatory signal obtained by contacting said HBV polynucleic acid and said oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 180 encoding a methionine from a codon 180 encoding a leucine.

39. (Previously Presented) The diagnostic kit according to claim 28 wherein at least one of

said oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 204 encoding a serine from a codon 204 encoding a methionine, valine or isoleucine is attached or immobilized to a solid support and

said oligonucleotide capable of discriminating, in said HBV polynucleic acid, a codon 180 encoding a methionine from a codon 180 encoding a leucine is attached or immobilized to a solid support.

40. (new) A method for screening for drugs active against an HBV virus comprising a polynucleic acid according to claim 1 or comprising a protein according to claim 6, said method comprising:

- (i) measuring replication of said HBV virus in the absence of said drug;
- (ii) measuring replication of said HBV virus in the presence of said drug;
- (iii) inferring from (i) and (ii) the inhibitory effect of said drug on replication of said HBV virus.